REMARKS

A check in the amount of $225.00 for the requisite fee for a two month extension of time is enclosed. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition

Claims 10-18, 32-36, 38, 41 and 42 are pending in this application. Claim 10 is amended to render it clear that the method includes a step of assessing the level of cell activation in a subject with a disease or condition, and that any treatment for cell activation is distinct from treatment from the disease or condition. Claims , 11, 13 and 15 are amended to reference proper antecedent in independent claim 10. Claim 32 is amended to render it clear that cell activation of white blood cells is measured, and that, if the subject has elevated activation level, therapies are undertaken or administered to lower the level of cell activation. Such lowering prevents (reduces the risk) of developing a disease or reducing the risk of a poor outcome of a treatment of a disease or disorder. No new matter is added. All claims affirmatively and unequivocally recite the step (1) measuring the level of cell activation, and (2) determining whether it is elevated.

ELECTION

The Examiner indicates that claims 17, 33 and 38 are withdrawn from consideration as being drawn to non-elected subject matter. Applicant respectfully submits the claims were subject to an election of species, not to a requirement for restriction. Applicant elected the species Futhan for search purposes. All pending claims are linked by generic claims, such as claims 10 , which links claim 17 with the elected subject matter, and claim 32, which links claims 33 and 38 with the elected subject matter. According to MPEP §809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on 1) specifying the linking claims; and 2) examining the linking claims with the elected group. The linking claims **must** be examined with the elected group, and the Restriction Requirement **must** be conditioned on allowability of the linking claims. If the linking claims are deemed allowable, then the Restriction Requirement must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined.

In this instance claims, such as claims 10, as well as claims 11-16, and claims 32 and dependent claim 42 are linking claims, linking claims 17 and claims 33 and 38, respectively, to the elected subject matter. Upon allowance of the linking claims, such as claims 10 and/or 32, claims 17, 33 and 38, the election as should be withdrawn and claims 17, 33 and 38 also should rejoined and should be allowable.

Furthermore, claims 17, 33 and 38 have been examined throughout the extensive prosecution of this application,. In fact, claims 17, 33 and 38 were included in the appealed claims. The claims 17, 33 and 38 have been examined were rejected under 35 U.S.C. §112, first and second paragraphs, as well as 35 U.S.C. §103(a). The rejections under 35 U.S.C. §103(a) were not maintained by the Examiner in the Examiner's answer; the rejections under 35 U.S.C. §112, were appealed and the Examiner was reversed. The Examiner has set forth no basis upon which to now withdraw claims 17, 33 and 38. Applicant fully intends to appeal again should the art rejections be maintained; and should not 9 years after filing the application and seven years into prosecution of the these claims be required to file a divisional directed to these claims. It is unfair, given the extensive file history existing requirement for restriction and full examination of claims 17, 33 and 39 to now withdraw these claims. The issues on appeal were applied to these claims. Clearly there can be no burden on the Office to continue to exam claims previously examined. It is quite unexpected for the Office to now withdraw claims that already were successfully appealed.

Had Applicant known that these claims would be withdrawn, Applicant could have filed a divisional application to the withdrawn claims years ago to avoid further patent term loss. Consequently, Applicant will argue the propriety of the rejections as they apply to claims 17, 33 and 38, and, if necessary, will include them among any appealed subject matter.

Summary of the claimed subject matter

The following is a brief discussion of the application to aid in appreciating the claimed subject matter. The instant application and claims are directed to methods in which the level of cell activation is employed as a therapeutic intervention point, a therapeutic indicator and/or a diagnostic/prognostic marker Figures 1-3 in the application provide an exemplary and schematic description of the use of cell activation as a marker and therapeutic intervention point. No art of record nor of which applicant is aware discloses, teaches or suggests using cell activation as point of therapeutic intervention or as a diagnostic indicator of any sort.

Cell Activation as a point of therapeutic and/or diagnostic intervention

Cells in microcirculation can be encountered in a relatively quiescent state and in various stages of activation. As stated on page 16, line 21, - page 17, line 4, of the application, for example:

> Cell activation refers to changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces. For example, adhesion molecules and villi attach macrophage and monocytes to endothelium. Macrophage and monocytes may then infiltrate into tissue outside the blood vessel beginning the development of atherosclerosis, venous insufficiency ulcers an diabetic retinopathy.

Thus cell activation is a parameter that is marked by physical and metabolic changes in white blood cells. The level thereof can be assessed using assays that detect such physical and/or metabolic changes in white blood cells.

As described in the application, a certain level of cell activation is a normal physiological response that is essential for survival. Through the inappropriate stimulation of various defense strategies involving inflammatory cells and the immune system, an animal often is responsible for its own demise. The first inflammatory cells to be upregulated in these conditions are polymorphonucleated (PMN) cells, or neutrophils. These cells, which include 60% of the circulating pool of leukocytes in humans, constitute a formidable line of defense against invading pathogens. When activated, they produce a number of cytotoxic components including oxygen free radicals and proteases designed to destroy and degrade invading bacteria.

When unregulated, secreted leukocyte products also can kill cells in the body and destroy tissue. Inappropriate activation of such immune cells is implicated in the pathology of many disease processes (see, Section B of the application, for example). Cardiovascular complications, such as myocardial infarction, venous ulceration and ischæmia/reperfusion injury are associated with an activation of cells in circulation. Activated neutrophils release a number of toxic substances including free radicals, proteases and their products that kill cells and ultimately destroy tissues. Neutrophils also release cytokines and other inflammatory substances, resulting in the recruitment of additional neutrophils and activated cells, further propagating inflammation and injury.

Thus, as described and shown throughout the application (see, e.g., Section B, starting on page 20 and Figs. 1-3), inappropriate or excessive activation is related to certain acute and chronic diseases and poor disease and treatment outcomes. For example, Section B, page 20 et seq., of the application, describes that the activation of cells is linked to a variety of diseases, including myocardial infarction, hemorrhagic shock, general health and subclinical compromise thereof, diabetes, hypertension, and venous insufficiency as well as an array of other disorders.

The application (and the claims), then describe (and claim) the use of cell activation as point of therapeutic intervention or as diagnostic indicator or prognostic marker.

The rejected claims

The claims capture this subject matter and methods. In particular, the claims in this application are directed to methods of preventing diseases, improving treatment outcome and reducing risk by measuring cell activation level, and, if elevated, administering cell activation lowering therapy to lower the level of cell activation. The cell activation lowering therapy is selected to lower the level of cell activation, and is distinct from any treatment for any disease or disorder in a subject. As a prophylactic, the level of cell activation is measured, even in the absence of any symptoms, such as part of a routine physical, and, then if it is elevated, cell activation lowering therapy is administered or undertaken. The cell activation lowering therapy is undertaken, not for treatment of a particular disease, but to lower the level of cell activation. The claims do not read on bed rest, nor on methods of treating inflammation. The methods require an affirmative step of measuring the level of activation of white blood cells, determining whether or not the level are elevated, and, then, if they are elevated, undertaking or administering cell activation lowering therapy. As shown, in the application, treating inappropriate cell activation can improve outcomes for treatment of diseases and/or can be prophylactic. As recognized by the Examiner, when withdrawing the previous rejections over art, none of the cited art of record teaches or suggests such methods.

(a) Independent claim 10 and dependent claims **Claim 10** is directed to a method of improving treatment outcome or reducing risk of treatment for a disease or condition in a subject with a disease or condition. The method, as claimed, includes the steps of :

assessing treatment options for the disease or condition;

measuring the level of activation of white blood cells, in a subject with the disease or condition;

determining if the level is elevated; and,

if cell activation level is elevated, administering activation lowering therapy **prior** to commencing treatment for the disease or condition or **with** treatment for the disease or condition, **thereby improving treatment outcome or reducing risk of treatment**. Hence, cell activation-lowering therapy is distinct from any treatment for the disease or condition.

Dependent claim 11 specifies that cell activation is measured by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation. Claim 12 specifies that the disease or condition that the subject has is selected from cardiovascular disease, inflammatory disease, trauma, autoimmune diseases, arthritis, diabetes and diabetic complications, stroke, ischemia, Alzheimer's disease. Claim 13 specifies that the treatment for the disease or condition is surgery, treatment of unstable angina or treatment for trauma. Claim 14 specifies that activation lowering therapy comprises administering a protease inhibitor, dialysis, alterations in lifestyle to reduce stress, or alterations in diet. Claim 15 specifies that the protease inhibitor is a serine protease inhibitor, and claim 16 specifies that the protease inhibitor is selected from among α_1-proteinase inhibitor (α_1-antitrypsin), α_2-macroglobin, inter-α_1-trypsin inhibitor, and α_1-antichymotrypsin. Claim 17 specifies that the disease or condition is selected from among myocardial infarction, stroke, hemorrhagic shock, diabetic retinopathy, diabetes and venous insufficiency. Claim 18 specifies that the protease inhibitor in claim 14 is 6-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate (Futhan) or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof.

(b) Independent claim 32 and claims dependent thereon

Claim 32 is directed to a method for preventing a disease or disorder or reducing risk of having a poor outcome from treatment. The method includes the steps of:

> testing cell activation levels of white blood cells in a subject;
> determining if the level is elevated; and,
> if the white blood cell activation level is elevated, administering or undertaking cell activation lowering therapy to lower the levels of cell activation, thereby **preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.**

Claim 33 specifies that the activation lowering therapy comprises modifications in diet and/or lifestyle. Claim 34 specifies that activation lowering therapy comprises administration of a protease inhibitor. Claim 35 specifies that the protease inhibitor is a serine protease inhibitor and claim 36 specifies that the protease inhibitor is selected from among α1-proteinase inhibitor (α1-antitrypsin), α2-macroglobin, inter-α1-trypsin inhibitor, and α1-antichymotrypsin. Claim 38 specifies that activation lowering therapy comprises dialysis. Claim 41 specifies that the protease inhibitor in the method of claim 35 is 6-amidino-2-naphthyl p-guanidino-benzoate dimethanesulfonate or a pharmaceutically acceptable salt, acid, ester and other derivatives thereof. Claim 42 recites that cell activation is assessed by assays that measure one or more of the level of free radical production, pseudopod formation, adhesion molecule expression and degranulation.

THE REJECTION OF CLAIMS 10-16, 32, 34-36 AND 42 UNDER 35 U.S.C. §102

Claims 10, 12, 13 and 32

Claims 10, 12, 13 and 32 are rejected under 35 U.S.C. §102(b) as anticipated by Adams *et al.*, which allegedly discloses that the response of inflammatory cells to immunollogic activation is release of newly formed products that alter the function and biochemistry of surrounding cells and tissues, so that so that all subjects experiencing inflammation will have elevated levels of inflammatory mediators. The Examiner sates that Adams *et al.* proposes to treat inflammation with compounds to reduce inflammation. The Examiner states that the claims read on a "subject recognizing that the subject is experiencing inflammation." This rejection is respectfully traversed. As discussed below, the claims **do not** read on a subject noting that they subject has inflammation and treating it.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15

USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

Rejected claims

As discussed above, claim 10 requires two one measurement (the level of activatio9n of white blood cells) and two treatments (cell activation lowering therapy and treatment for the disease or condition). Claim 10 is directed to a method for improving treatment outcome or reducing risk of treatment for a disease or condition, by

(1) assessing treatment options for treatment of a disease or condition in a subject;
(2) measuring cell activation level in a subject with the disease or condition; and,
(3) if cell activation level is elevated, administering activation lowering therapy prior to commencing treatment for the disease or condition or with treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment; and
(4) administering treatment for the disease or condition.

Hence, claim 10 is directed to methods for improving treatment outcome or reducing risk of treatment, and includes four steps and two treatments (one conditional). This claim captures embodiments described in the application in which it has been observed that patients with seemingly similar conditions and health, when treated, have very different outcomes. As shown in application this difference can be attributed to the level of cell activation. Patients with higher level of cell activation have poorer outcomes. Hence, can be treated to lower level of cell activation before undertaking treatment for the disease or condition, or with the treatment (particularly in an emergency setting). Dependent claims are discussed above.

Independent claim 32 is directed to a method for preventing a disease or disorder or reducing risk of having a poor outcome from treatment. The method includes the steps of:

> testing cell activation levels of white blood cells in a subject; and,
> if the white blood cell activation level is elevated, administering or undertaking cell activation lowering therapy to lower the levels of cell activation, thereby preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.

Claim 32 as previously pending and as amended for clarity, does not read on bed rest nor on administering an inflammatory. It requires affirmative steps of testing the level of activation of white cells; determining if their level of activation is elevated, and, if the levels are elevated, then administering therapy to lower the level of cell activation. Hence the claim does include a requirement for a step of testing white blood cells, and thus, cannot read on best rest nor on administering an anti-inflammatory. Claim 32 requires an affirmative step of testing the activation levels of the white blood cells of a subject to determine whether they are elevated, and, then, if elevated, administering or undertaking cell activation lowering therapy. The steps of testing the level of activation and then determining if the levels are elevated cannot be ignored.

Disclosure of Adams *et al.*, and differences from the claims

Adams *et al.* provides compounds for treating inflammatory disorders and methods of treatment in which the compounds are administered. Adams *et al.* does not disclose any methods that include measuring the level of activation of white blood, and a determining whether the level is elevated. Adams *et al.* does not disclose any methods for improving treatment outcome or reducing risk of treatment.

The Examiner urges that the specification or claims do not require a blood test or other procedure to assess cell activation. This is unequivocally not correct. Claims 10 and 32 recites "measuring"; measuring implies or connotes a test or assay As stated above, there is no reason to ignore the steps of the method requiring such action. The application defines cell activation with reference to the properties of white blood cells, and then describes exemplary tests to measure it. Nothing in the specification discloses, suggests or otherwise implies that assessment is other than a rigorous measurement, such as an assay. In fact, the application specifies that a test is employed. For example, the first sentence in the Summary states:

> **SUMMARY OF THE INVENTION**
>
> Diagnostic methods that rely on the use of one or more assays that assess cellular activation are provided. . . .
>
> The assays are performed on whole blood or leukocytes, and indicate singly or in combination the level of cardiovascular cell activation, which is

pivotal in many chronic and acute disease states. The cellular activation may be assessed by any assays known to those of skill in the art, such as those exemplified herein, that are used to measure cellular activation. For example, cell activation may be assessed superoxide production, such as defined by the nitroblue tetrazolium test and lucigenin-enhanced chemiluminescence, and/or actin polymerization, such as defined by the pseudopod formation test, are indicators of cellular activation levels.

Assays are performed on whole blood or leukocytes and indicate, individually or in combination the level of cardiovascular cell activation. The results of the assays can be used within a clinical framework to support therapeutic decisions, including but not limited to: further testing for infectious agents; anti-oxidant or anti-adhesion therapy; postponement and optimal re-scheduling of high- risk surgeries; classifying susceptibility to and progression rates of chronic disease such as diabetes, atherogenesis, and venous insufficiency; extreme interventions in trauma . . ..

The results of specific cell activation assays are used in guiding therapeutic decisions such as, but not limited to: further testing for infectious agents, anti-oxidant or anti-adhesion therapy, postponement and optimal re-scheduling of high- risk surgeries, classifying susceptibility to and progression rates of chronic disease such as diabetes, atherogenesis, and venous insufficiency; extreme interventions in trauma cases of particularly high risk and activation-lowering therapies.

The specification in section C states:

Tests for detecting cell activation

In practicing the method, one or more tests for cell activation would be performed. These tests, discussed and exemplified below in more detail below and include tests that assess indicators of activation, such as changes in shape and free radical production. For example cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques. Superoxide anion production can be detected and quantified using chemiluminescence generating reagents, such as luminol, isoluminal and lucigenin, that quantitatively react therewith. Free radicals can be assessed by NBT (nitroblue tetrazolium). Adhesion can be assessed by various immunoassays that detect surface adhesion molecules, such as CD11, CD18 and L-selectin and others. Other indicators of activation include expression of certain factors, such as interleukin and TNF-α, which can be measured by known immunoassays.

Activation can also be assessed by sampling plasma and determining whether it activates cells, such as endothelial cell cultures. Plasma can be tested for clastogenic activity by standard methods. Although there is a high correlation between the different cell activation assay measures, it is likely that there will be different combinations of indicators which are most informative in any situation. For example,

> plasma activator levels might be high but circulating activated neutrophil counts low due to sequestration of the activated cells in the microcirculation. Also, genetic, age, and environmental differences between patients will complicate the interpretation of the assays. Clinical tests are in preparation to relate statistically cell activation measures to disease outcomes, to find the formulas which are invariant to patient differences, and to establish the best predictive procedures and activation lowering therapies in different situations. The measurement of cell activation and circulating plasma factors also serves as an effective tool to evaluate the effectiveness of new interventions prior to execution of full-scale clinical trials. Drug candidates thereby may be rejected, or patient populations enriched for more favorable response to the candidate drug.

Section E of the application describes exemplary ways to measure the level of cell activation:

> Rates of free radical production in whole blood can be measured using phenol red (Pick et al. (1980) J. Immunol. Methods 38:161-170) or other dye forming reagents (U.S. Patent No. 5,518,891). Intracellular radical production may be measured with nitroblue tetrazolium (NBT) reduction or chemiluminescence (Cheung et al. (1984) Aust. J. Expt. Biol. Med. Sci. 62:403) assays. Radical production in whole blood or plasma may be measured electrochemically, and mRNA expression of specific genes can be quantitated, for example, using Northern blots or DNA microarrays.
>
> Expression of adhesion molecules such as CD11b, CD18, and of L-Selectin can be quantitated via flow cytometry, while cytokines and chemokines, such as interleukins and TNF-a can be quantitated with immunoassays.
>
> Cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques.
>
> Blood plasma is known to carry cell activation factors in response to specific events. Plasma from I/R episodes including MI (Chang et al. (1992) Biorheology 29:549-561) and hemorrhagic shock (Elgebaly et al. (1992) J. of Thoracic and Cardiovascular Surgery 103(5):952-959; Paterson et al. (1993) Am. Vasc. Surg. 7(1):68-75; Barroso-Aranda et al. (1995) J. Cardiov Pharmacology 25(Suppl 2):S23-S29) activates neutrophils, as does plasma from smokers' blood (Pitzer et al. (1996) Biorheology 33(1):45-58). Patient blood samples can be applied to standard donor cells and the response of the donor cells used as a measure of the potency of the circulating activating factors in the patient blood.

Working examples that include tests for cell activation levels are included in the application. Thus, it is clear that the specification and claims "require a blood test or other procedure to assess cell activation."

The Examiner also states that "Adams is treating trauma since as noted by Groutas,

inflammation is associated with tissue trauma, see Groutas, column 1, lines 10-20." The relevance of this statement is unclear, since claim 10 and its dependent claims (as well as independent claim 32 and its dependent claims) affirmatively recite testing the level of activation of white blood cells. Claim 10, which is directed to a method for improving treatment outcome or reducing risk of treatment for a disease or condition, requires measurement of cell activation, determination whether the level is elevated, administration of ell activation lowering therapy, if the level of cell activation is elevated, **and,** treatment for disease or condition. Hence claim 10 includes the affirmative steps of measuring the level of cell activation and determining if the level is elevation, and also two treatments if cell activation level is elevated. Independent claim 32 is directed to methods for preventing a disease or disorder or reducing risk of having a poor outcome from treatment, similarly requires affirmative steps of measuring cell activation and determining if the level is elevated. If the level is elevated cell activation lowering therapy undertaken or administered.

Adams *et al.*, does not disclose a method for improving treatment outcome or reducing risk of treatment for a disease or condition (claim 10) or reducing the risk of developing a disease or condition or of having a poor outcome from treatment (claim 32) by testing the level of cell activation, and determining whether it is elevated. If elevated, administering or undertaking cell activation lowering therapy. Claim 10 recites that treatment for a disease or condition is initiated with or after cell activation lowering therapy. Adams *et al.* does not disclose a method involving treatments for an elevated level of cell activation and for a disease or a condition. Adams *et al.* simply does not disclose a method including steps of measuring the level of activation of white blood cells and determining whether it is elevated, nor does it does disclose cell activation lowering therapy as a treatment to lower the level of cell activation distinct from treatment for a disease or condition, whether it is inflammation, trauma or both. Therefore, Adams *et al.* does not disclose all steps of the method as claimed, and does not anticipate any pending claim.

Claims 10, 12-16, 32 and 34-36

Claims 10, 12-16, 32, and 34-36 are rejected under 35 U. S. C. 102(b) as being anticipated by Groutas *et al.*, which allegedly discloses that inflammation is associated with tissue trauma and that that alpha-l -proteinase inhibitor is administered to reduce inflammation (column 1, lines l-45). The Examiner states: "as with the teachings of Adams as noted by the Board, the administration of alpha-l -proteinase will also treat the

inflammation within the scope of the claims." The Examiner further states that the Board stated that neither the specification nor claims require a blood test or other "procedure" for assessing cell activation, so that the claims allegedly read "on a subject recognizing that the subject is experiencing inflammation." This rejection respectfully is traversed.

Relevant law

See above.

The rejected claims

The claims are discussed above. As noted claim 10 is directed to methods for improving treatment outcome or reducing risk of treatment for a disease or condition. Claim 32 is directed to methods for preventing a disease or disorder or reducing risk of having a poor outcome from treatment. In both claims, the methods include the steps of measuring the level of activation of white blood cells is elevated, and determining whether the level is elevated. If elevated cell activation lowering therapy is administered or undertaken. In claim 10, treatment for a disease or condition is administered with or after the cell activation lowering therapy. In claim 32, the cell activation lowering therapy is administered or undertaken to reduce the risk of developing a disease or the reduce the risk of a poor outcome of treatment. In all claimed methods, cell activation lowering therapy is administered or undertaken with or before any other treatment.

Disclosure of Groutas *et al.* and differences from the claimed methods

Groutas *et al.* discloses isothiazolidin and isothiazsolidine compounds and their use as anti-inflammatories to treat inflammation. Groutas *et al.*, does not disclose any methods that include the steps of measuring the level of activation of white blood cells; determining whether the level is elevated; and, if elevated, administering or undertaking cell activation lowering therapy. Groutas *et al.* does not disclose any methods in which cell activation lowering therapy is administered before or with therapy for a particular disease, nor any methods in which the level is measured.

Analysis

First, as discussed above, the Board was not correct in its assessment of the subject matter of the claims. The rejections over art were not on appeal as arguments presented in the Appeal Brief were persuasive, and dropped by the Examiner. Hence, the Board's statements address issues not before it. The Board did not have the opportunity to evaluate the claims in that context.

In fact, each of independent claims 10 and 32 require **affirmative steps** of measurement of the level of activation of white blood cells, and a determination of whether the level is elevated, and then, if elevated, undertaking or administering cell activation lowering therapy to lower the level cell activation, not to treat any disease a subject may have. None of the references discloses a method that includes a step of measuring the level of activation of white blood cells nor measuring its level and determining whether it is elevated.. None disclose measuring the level, administering cell activation lowering therapy if the levels are elevated prior to or with the treatment for the disease as required by claim 10, or prior to any treatment or as a prophylactic as required by claim 32.

In particular, Groutas *et al.* does not disclose any methods including the steps of measuring the level of activation of white blood cells is elevated,; determining whether the level is elevated; and if elevated cell activation lowering therapy is administered or undertaken. Groutas *et al.* does not disclose any methods in which cell activation lowering therapy is administered before or with therapy for a particular disease. Therefore, Groutas *et al.* does not anticipate any pending claims.

Claims 10, 11, 32 and 42

Claims 10, 11, 32 and 42 are rejected under 35 U. S. C. 102(e) as being anticipated by Rabkin et al., which allegedly discloses assays for measurement of free radical production, such as colorimetric assays. The Examiner then states:

> Thus, when administering such compounds of Rabkin one can assess the damage of a disease/condition by assessing the free radical production as taught by Rabkin (column 9, lines 40-50). Note also that Rabkin teaches that his invention could be administered to someone who has inflammatory disorders, see column 2, lines 40-60.

The Examiner, then states that the Board had [incorrectly] stated that the claims do not require a blood test or other "procedure" be used to assess cell activation, so that the claims allegedly "read on a subject recognizing that the subject is experiencing inflammation." This rejection respectfully is traversed.]

Disclosure of Rabkin *et al.* and differences from the claimed methods

Rabkin *et al.* disclosed compounds, compositions and methods for the amelioration of cell death due to necrosis or apoptosis. Cell necrosis or apoptosis are disclosed to accompany various diseases and disorders, and also may be associated with various therapeutics, such as cocaine and AZT. that accompany various disease. Hence Rabkin *et al.* discloses anti-necrotic compounds that reduce cell death. At column, 9, Rabkin *et al.* discloses that its

compounds can be used to reduce cell death caused by therapeutics that cause oxidative stresses, leading to cell death. The effects of the therapeutics can be assessed by measuring free radical production. The compounds of Rabkin *et al.* are for ameliorating cell necrosis or apoptosis, **not** oxidative stress. In such instances, the compounds of Rabkin *et al.* are administered after treatment with the therapeutic, such as AZT.

Hence Rabkin *et al.* discloses methods in which compounds that reduce cell death or apoptosis are administered. Rabkin *et al.* discloses that cell death is associated with numerous disorders and also administration of various therapeutics. Rabkin *et al.* discloses that its compounds can be administered following administration of therapeutics that cause oxidative stress, which leads to cell death or apoptosis. Rabkin *et al.* discloses that oxidative stress can be assessed by measuring cell activation levels. The compounds are **not** administered **before therapy** for a disease or condition.

Rabkin *et al.*, **does not** disclose methods in which the level of activation of white blood cells is measured, and, a determination made whether or not the level is elevated. Rabkin *et al.* does not disclose then administering or undertaking therapy to lower the levels of activated white blood cells, where such is undertaken prior to or with therapy for a particular disease or condition (claim 10), or is undertaken or administered prophylactically (claim 32) to lower cell activation levels and thereby reduce the risk of developing disease (claim 32) or conditions or suffering adverse effects that are associated with elevated levels of cell activation. Rabkin *et al.* provides compounds that are anti-apoptotic or anti-necrotic agents **and** that are administered to reduce cell death associated with a disease or condition or are administered **consequent** to administration of certain therapeutics, **not before** administration of any therapeutics.

Rabkin *et al.* does not disclose the methods of claim 10, since it does not disclose a method in which the level of activation of white blood cells is measure and a determination made whether the level is elevated, and if the level is elevated, administering cell activation lowering therapy, before or with therapy for a disease or condition. Rabkin *et al.* provides compounds that reduce cell death, not reduce cell activation; Rabkin does not assess the level of cell activation and if elevated administer cell activation lowering therapy, and does not administer it before administering a therapeutic for a disease or condition, as a way to reduce poor treatment outcome. Rabkin *et al.* administers its compounds to reduce cell death.

Similarly, Rabkin *et al.* does not disclose the methods of claim 10, since it does not

disclose a method in which the level of activation of white blood cells is measure and a determination made whether the level is elevated, and if the level is elevated, administering cell activation lowering therapy. Rabkin *et al.* makes not mention of cell activation lowering therapy for any purpose, and certainly does not disclose a method in which cell activation

Therefore, Rabkin *et al.* does not disclose all steps of each method as claimed. Thus, Rabkin *et al.* does not anticipate any pending claim.

Claims 10, 11, 32 and 42

Claims 10, 11, 32 and 42 are rejected under 35 U. S. C. 102(b)as being anticipated by WO 92/15707, which discloses that free radical production is assayed by using immunoassay methods, see abstract, page 20, line 15-page 21, line 10, and "uses its compositions to prevent inflammatory diseases, see abstract." WO 92/15707 is alleged to states that this approach permits "actions to avoid the pathogenic potential of these antibodies, but the detection serves in itself as a sensitive measure of ongoing oxidative damage." Detection of such antibodies may be used as the basis for modifying or terminating certain therapies or avoiding certain exposure risks (page 20, line 15-page 21, line 10). This rejection respectfully is traversed.

Disclosure of International PCT application No WO 92/15707 and differences from the claimed methods and analysis

PCT application No WO 92/15707 discloses immunoassay methods for detecting antibodies that are specific for oxidized DNA, which can be used for diagnosing certain inflammatory diseases and for monitoring therapy for such diseases. In particular, PCT application No WO 92/15707 discloses that certain diseases, such as systemic lupus erythematosus SLE, cause formation of strand breaks in DNA and oxidation of DNA bases against which autoantibodies form. Sera of patients suspected of having SLE or other inflammatory diseases contain antibodies that recognized oxidized DNA bases. The methods in PCT application No WO 92/15707 detect the autoantibodies. Hence PCT application No WO 92/15707 discloses assays for diagnosing SLE and other such diseases in which oxidized DNA bases and autoantibodies thereto are produced.

PCT application No WO 92/15707 does **not** disclose measuring the levels of activation of white blood cells, nor methods of determining whether such levels are elevated, and, if elevated administering or undertaking cell activation lowering therapy. Measurement of oxidized DNA bases or autoantibodies thereto is not disclosed as a measure of the level of activation of white blood cells. Hence PCT application No WO 92/15707 does

not disclose using the level of activation of white blood cells as a therapeutic or diagnostic point of intervention before or during treatment of a disease or condition, or prior to treatment or as a prophylactic. The methods of PCT application No WO 92/15707 are for diagnosing diseases, such as SLE, that involve oxidative damage to DNA.

Therefore, PCT application No WO 92/15707 does not disclose all elements as claimed. Thus, PCT application No WO 92/15707 does not anticipate any pending claims.

The REJECTION OF CLAIMS 10, 12-16, 18, 32, 34-36 AND 41 UNDER 35 U.S.C. §103(a)

Claims 10, ,12-16, 18, 32, 34-36, 41 are rejected under 35 U. S. C. 103 as being obvious over Groutas in view of JP 409040579 because Groutas teaches that inflammation is associated with tissue trauma and that alpha-1-proteinase inhibitor is administered to reduce inflammation (col. 1, lines 1-45). The Examiner concludes that, as with Adams *et a.* "administration of alpha-1-proteinase will also treat the inflammation within the scope of the claims." Groutas does not teach that futhan (nafamostat mesilate) is used as the specific protease inhibitor. JP teaches that nafamostat mesilate is known to be used to treat inflammation, specifically inflammatory bowel disease so that it "would have been obvious to have used futhan instead of alpha-l -proteinase since they both were known to treat inflammation at the time the invention was made and it clearly would have been within the purview of one of ordinary skill in the art to use either alpha-1 proteinase or futhan to treat inflammation" since JP '579 teaches that the medicine (the fibrin paste containing the nafamostat mesilate-futhan) suppresses relapse and keloplasty in the postoperative anastomosed part of the inflammatory bowel disease "thus motivating one of ordinary skill in the art to use the nafamostate mesilate instead of using of the alpha-1 proteinase. Again the Examiner notes that the claims fail to require a "blood test or other procedure" to assess cell activation. The Examiner again states, incorrectly, that the claims fail to require a "blood test or other procedure" to assess cell activation. This rejection respectfully is traversed.

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention.

Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 U.S.P.Q. 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" (*In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. 871, 881 (CCPA 1981)), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983). Importantly, **all claim limitations** must be taught or suggested by the prior art to establish that claims are *prima facie* obvious. *See, e.g.,* MPEP 2143.03 and *In re Lowry*, 32 F.3d 1579, 32 U.S.P.Q.2d 1031 (Fed. Cir. 1994), citing *In re Gulack*, 703 F.2d 1381, 217 U.S.P.Q. 401 (Fed. Cir. 1983), citing *In re Royka*, 490 F.2d 981, 180 U.S.P.Q.2d 580 (CCPA 1974).

Analysis

Teachings of the Cited References and differences from the claimed methods

Groutas *et al.* teaches isothiazolidin and isothiazolidine compounds and their use as anti-inflammatories to treat inflammation. Groutas *et al.*, does not teach any methods including the steps of measuring the level of activation of white blood cells is elevated; determining whether the level is elevated; and if elevated cell activation, administering or undertaking cell activation lowering therapy. The compounds of Groutas *et al.* are administered as the treatment for a disease, not for cell activation lowering therapy following a determination that cell activation level is elevated. Groutas *et al.* does not disclose any methods in which cell activation lowering therapy is administered before or with therapy for a particular disease. Groutas *et al.* does not teach or suggest that cell activation is a point of therapeutic intervention or diagnosis. Hence, Groutas *et al.* fails to teach any elements of any pending claims.

JP 409040579 teaches administration of futhan for treatment of inflammatory bowel disease. Futhan is administered as the treatment for a disease, not for cell activation lowering therapy following a determination that cell activation level is elevated. JP

409040579 does not cure the deficiencies in the teachings of Groutas *et al.* Furthermore, Groutas *et al.* is specifically directed to particular compounds, so the combination of teachings of Groutas *et al.* could never result in substitution of the futhan for the compounds of Groutas *et al.*, since Groutas *et al.* is directed to its own compounds and uses thereof.

Analysis

The combination of teachings of the cited references does not result in any of the claimed methods

Neither reference, nor any combination thereof, teaches or suggests a method of improving treatment outcome or reducing risk of treatment, nor a method that includes any of the steps of measuring cell activation level, determining whether the level is elevated, and, if elevated administering cell activation lowering therapy prior to or with administering treatment for a disease or disorder (claim 10 and dependents) or prophylactically to reduce risk of treatment (claim 32 and dependents). The combination of teachings of the cited references fails to teach or suggest any steps of the methods as claimed.

The Examiner is stating that the claims do not recite an affirmative step of measuring cell activation level, and then is equating treatment of inflammatory diseases with treatment for lowering cell activation. It respectfully is submitted that the claims **unequivocally** require a step of measuring the level of cell activation, and a step of determining whether it is elevated. Neither reference teaches such steps. Further neither references teaches or suggests treatment for lowering cell activation. Inflammatory disease is not synonymous with cell activation. Cell activation as discussed above, and in application, is a precursor, typically a silent, symptomless precursor, to a variety of diseases and also as a cause of poor treatment outcome. As stated on page 16, line 21, - page 17, line 4, of the application, for example:

> Cell activation refers to changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces

Cell activation, as described in the application can result in a host of disorders; it is not the same as inflammatory disease. The use of futhan for treating cell activation is a **new** use for futhan, previously used for treating inflammatory diseases, such as IBD.

These references fail to teach or suggest a method of improving treatment outcome or reducing risk of treatment, by assessing treatment options for a disease or condition by

measuring cell activation levels in a subject; and, if elevated, administering activation lowering therapy prior to commencing or with further treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment; nor a method of prophylaxis, diagnosis and treatment by assessing cell activation; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

None of these references, singly nor in any combination, teaches a step of measuring cell activation levels to assess whether they are elevated, nor a method in which if cell activation levels are elevated, initiating cell activation lower therapy. In all references in which futhan is administered, it is administered as the treatment for a disease, not for cell activation lowering therapy, and certainly not following assessment of cell activation to determine if the level is elevated. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

The Combination of teachings References to result in any claimed method is based on the impermissible use of Hindsight

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983).

As noted, teachings of the combination of references do not result in the instantly claimed methods. For the combination of teachings to result in the methods as claimed, would requires use of the teachings of the application at issue and would need to include such teachings. To produce the claimed methods, requires picking and choosing portions of methods taught in the cited references, combining them as claimed in the application and adding teachings of the instant application. Hence claimed methods are not prima facie obvious because the combination of teachings of the references does not result in the instantly claimed methods absent use of the instant application in combination therewith.

For example, it is inappropriate for the Examiner to pick the part of the methods of Groutas *et al.* in which its compounds are administered for treatment of inflammatory disease or metastatic disease and then state the one of ordinary skill in the art would have substituted the futhan of JP '579, which teaches the use of futhan for treating IBD. Neither reference teaches nor suggests measuring cell activation levels, determining whether the level

is elevated, and if elevated administering or undertaking therapy to lower cell activation level, not to treat inflammatory disease. None of the references teaches assays for measuring cell activation, determining if the level is elevated, and then, if elevated, administering treatment to reduce cell activation. None teaches or suggests that futhan lowers cell activation levels. Therefore, the Examiner has improperly relied on hindsight in setting forth the rejection, has failed to recognize the actual elements of the claimed methods, and has failed to set forth a *prima facie* case of obviousness.

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In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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